16 December 2022
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Ebvallo (allogeneic Epstein-Barr virus specific cytotoxic T lymphocytes)

Treatment of post-transplant lymphoproliferative disorder

EU/3/16/1627

Sponsor: Atara Biotherapeutics Ireland Limited

Note: Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted

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1. Product and administrative information

Product	
Designated active substance(s)	Allogeneic Epstein-Barr virus specific cytotoxic T lymphocytes
Other name(s)	-
International Non-Proprietary Name	Tabelecleucel
Tradename	Ebvallo
Orphan condition	Treatment of post-transplant lymphoproliferative disorder
Sponsor's details:	Atara Biotherapeutics Ireland Limited Arthur Cox Building 10 Earlsfort Terrace Dublin 2 D02 T380 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Wainwright Associates Limited
COMP opinion	18 February 2016
EC decision	21 March 2016
EC registration number	EU/3/16/1627
Post-designation procedural history	
Sponsor's name change	From Wainwright Associates Limited to PharmaLex UK Services Limited – EC letter of 11 November 2016
Transfer of sponsorship	From PharmaLex UK Services Limited to Atara Biotherapeutics Ireland Limited – EC decision of 21 January 2017
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Egbert Flory / Romaldas Mačiulaitis
Applicant	Atara Biotherapeutics Ireland Limited
Application submission	5 November 2021
Procedure start	25 November 2021
Procedure number	EMA/H/C/4577/0000
Invented name	Ebvallo

Proposed therapeutic indication	Treatment of Epstein-Barr virus positive post-transplant lymphoproliferative disease Further information on Ebvallo can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/ebvallo
CHMP opinion	13 October 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Karri Penttila / Frauke Naumann-Winter
Sponsor's report submission	3 December 2021
COMP discussion	4-6 October 2022
COMP opinion (adoption via written procedure)	19 October 2022

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2016 was based on the following grounds:

The sponsor Wainwright Associates Ltd submitted on 29 October 2015 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing allogeneic Epstein-Barr virus specific cytotoxic T lymphocytes for treatment of Epstein-Barr Virus-associated lymphoproliferative disorder following allogeneic haematopoietic cell transplant (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

For the purpose of orphan designation, the Committee for Orphan Medicinal Products (COMP) considered that the condition originally proposed by the sponsor should be renamed as "post-transplant lymphoproliferative disorder" (hereinafter referred to as "the condition") based on the current classification.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing allogeneic Epstein-Barr virus specific cytotoxic T lymphocytes was considered justified based on clinical data demonstrating improved overall survival of persons affected by the condition;
- the condition is life-threatening due to fulminant and lethal course of the disease and chronically debilitating due to transplant specific organ dysfunction, malaise, lethargy, weight loss and fever;
- the condition was estimated to be affecting approximately 1.6 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing allogeneic Epstein-Barr virus specific cytotoxic T lymphocytes as an orphan medicinal product for the orphan indication: treatment of post-transplant lymphoproliferative disorder.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Post-transplant lymphoproliferative disorder (PTLD) is a heterogeneous clinical and pathological group of life-threatening lymphoid disorders ranging from benign polyclonal B-cell proliferation to malignant lymphomas, which arise in the context of immunosuppression following solid organ transplantation (SOT) or allogeneic haematopoietic stem cell transplantation (HCT).

The majority of cases in the western world are derived from B lymphocytes and are Epstein–Barr virus (EBV)-associated, particularly in the first year post SOT. EBV-negative cases account for approximately 20–40% of PTLD and usually occur after the first year of transplantation, with a second peak of incidence occurring at 10 years (Caillard S et al. 2017; Petrara MR et al. 2015).

EBV is a gamma human herpes virus with a prevalence of >90% in adults (Ball et al., 2015). EBV infects B lymphocytes and possibly oropharyngeal epithelial cells. Once the initial infection is brought under control, EBV latency persists lifelong in memory B lymphocytes. In patients who are immunocompromised due to congenital or acquired immunodeficiency syndromes, or iatrogenic immunosuppression associated with SOT (Prockop and Vatsayan 2017) or allogeneic HCT (Sutrave et al. 2018), loss of control over EBV can lead to a range of PTLDs including plasmacytic hyperplasia, infectious mononucleosis PTLD, florid follicular hyperplasia, polymorphic PTLD, monomorphic PTLD and classical Hodgkin lymphoma PTLD.

The commonest symptoms of PTLD are constitutional (fever, malaise) combined with a rising EBV DNA titre in the peripheral blood (patients are routinely monitored for EBV titres by blood tests post–transplantation) and markers of systemic inflammation.

PTLDs are sub-classified into four histopathological categories, namely non-destructive, polymorphic, monomorphic, and classical Hodgkin lymphoma.

The condition has not changed in terms of classification or description since the initial designation.

The approved therapeutic indication "*Ebvallo is indicated as monotherapy for treatment of adult and paediatric patients 2 years of age and older with relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) who have received at least one prior therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate*" falls within the scope of the designated orphan condition "Treatment of post-transplant lymphoproliferative disorder".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

Post-transplant lymphoproliferative disorders (PTLD) are lymphoid and/or plasmacytic life-threatening proliferations that occur in the setting of SOT or allogeneic HCT as a result of immunosuppression. They are among the most serious and potentially fatal complications of transplantation. The majority is related to the presence of Epstein-Barr virus (EBV). The condition is associated with high mortality rates with and without treatment. In one of the most recent reports, mortality of the condition amounted to 20% at 1 year, 44% at 5 years and 49% at 10 years (Steiner et al (2018)).

Lymphadenopathy is often absent, and symptoms are usually due to interference with the function of involved organs. Classic B symptoms such as pyrexia, sweats, and weight loss can occur. Clinical features of PTLD are often non-specific, while extra nodal involvement is common, including gastrointestinal tract (GIT), lungs, skin, bone marrow (BM), and central nervous system (CNS). Rarely, BM involvement can be the only disease site.

The clinical course of EBV-PTLD is fulminant, especially after failure of initial treatment. In the SOT setting, up to one-third of patients fail initial treatment (Jagadeesh 2020, Trappe 2017). In the HCT setting, approximately 50% of PTLD cases fail initial treatment (Garcia-Cadenas 2019).

In particular, patients with Epstein-Barr Virus–Positive Posttransplant Lymphoproliferative Disease (EBV+PTLD) following HCT who failed rituximab have a median OS of 1.7 months (Socié 2020) and patients with EBV+PTLD following SOT who failed chemotherapy after initial rituximab treatment have a median OS of 3.3 months (Zimmermann 2019). This poor prognosis has been recently confirmed in an expanded population with a median OS of 0.7 month (Sanz-Caballer 2021) and 4.1 months (Dharnidharka 2021) respectively in the HCT and the SOT settings.

Based on this clinical picture, PTLD disease is regarded a life-threatening and chronically debilitating condition and there have been no changes in the nature of the condition since the designation stage.

Number of people affected or at risk

At time of initial orphan designation in 2016, the COMP concluded that the condition was estimated to be affecting approximately 1.6 in 10,000 persons in the European Union. This reflected Epstein-Barr Virus (EBV) related PTLD in allogeneic HCT and SOT patients, and PTLD derived from other aetiologies (i.e., non-EBV related PLTD).

For this review the prevalence was estimated to be less than 0.5 per 10,000.

The sponsor performed an updated comprehensive Structured Literature Review (SLR) to determine the prevalence of PLTD in the EU, in accordance with the Meta-analysis of Observational Studies in

Epidemiology (MOOSE) guidelines and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Methodology for this SLR was aligned with that outlined by the Cochrane Collaboration and National Institute for Health and Care Excellence (NICE). Literature searches were performed using the Ovid platform to identify peer-reviewed articles and conference proceedings indexed in the relevant databases. A range of Medical Subject Heading (MeSH) terms and keywords were used. The epidemiology and treatment pattern reviews were limited to articles published from 2010 onward, as it would provide a more accurate view of the current epidemiology and treatment patterns. After identification of records and subsequent screening, a total of 183 total citations were included in the SLR.

The overall prevalence estimate is based on the combination of HCT PTLD, and SOT PTLD estimates.

Prevalence of HCT PTLD

Based on the reported SLR, 14 studies reported incidence data for PTLD patients undergoing HCT. All HCT studies reported cumulative incidence over a specified time frame; no studies reported incidence rates per 100,000 population.

Three (3) studies reported incidence estimates for transplant recipients in Europe, which ranged from 0.8% in a Spanish study of 12,641 transplant recipients over a median follow-up of 58 months (Garcia-Cadenas 2019) to 4% in a Swedish study of 1,021 transplant recipients between 1996 and 2011 (Uhlin 2014). The key literature identified to support an updated estimated incidence (and prevalence) for HCT are Dierickx et al and Garcia-Cadenas et al as published in 2013 and 2019 respectively (Dierickx 2013, Garcia-Cadenas 2019).

The prognosis of PTLD from HCT is poor with only 28% remaining alive at one year (Uhlin 2014). This permits the prevalence of PTLD to be estimated from the observed annual incidence of PTLD in the HCT population.

Based on the EU population, the updated prevalence of PTLD following HCT is estimated to be approximately 0.005 per 10,000 persons.

Prevalence of SOT PTLD

The sponsor presents the prevalence of PTLD post SOT based on two methodologies; the first method employs an epidemiological model from 2020, which is considered to provide a robust incidence (and prevalence) estimate at the present time; the second method uses the identical literature-based methodology in the original designation application in 2015, however, it includes an updated estimate for disease duration based on the current understanding of the condition.

This review will focus on the first method (i.e., epidemiological model) which is presented as primary, while the second method was considered as supportive.

In the SOT setting, PTLD can occur up to 30 years post-transplant and is largely dependent on the transplanted organ, the type and degree of immunosuppression, and patient characteristics (Trappe 2017, Dierickx 2013, Bishnoi 2017, Romero 2019). Nearly 80% of patients develop PTLD more than one year after transplant. The median time to PTLD following SOT is 9 years (0.2 - 27.9) (Trappe 2017). Further, the risk varies over time with highest risk during the first year following SOT. The highest cumulative incidence is in patients receiving multi-organ, heart, or intestinal transplants and the lowest is in patients receiving kidney transplants (Romero 2019).

Based on the SLR, a total of 110 studies reported on the incidence of PTLD among patients undergoing an SOT. Among which, 7 studies reported rates for European populations, ranging from 24 cases of

EBV- PTLD per 100,000 patients within the first one to five years following transplant to 454 cases of EBV+ PTLD per 100,000 patients within the first year of transplant (Olhom Vase 2015). According to the sponsor, large variation was observed in the incidence due to heterogeneity in the methodology and the study populations. Thus, the decision to construct a dynamic model that incorporates variables such as number of transplants in the past, annual incidence rate over time, and survival rate over time for transplant patients.

Population at risk and estimated new cases were incorporated into the model from available sources such as EU transplants since 2000 (Global Observatory on Donation and Transplantation, 2019), the rate of PTLD by organ type (Scientific Registry of Transplant Recipients, Kwong 2020) and the mortality over time (Graham 2020).

Based on the epidemiological model described, it is estimated about 750-900 new post-SOT PTLD cases occurred in the EU in 2019, with an approximate annual incidence of 0.018 per 10,000 persons. Assuming an average median overall survival of patients with PTLD following SOT as 9 years (Burns 2020, Trappe 2017, Jagadeesh 2020), the prevalence of PTLD in the SOT population is estimated to be 0.16 per 10,000 persons.

Concluding Estimate of Prevalence of PTLD

As in 2016, the overall prevalence estimate is based on the combination of estimates for HCT PTLD (0.005 per 10,000 persons) and SOT PTLD (0.16 per 10,000 persons). Additionally, the sponsor also presents an updated, literature-based calculation (as utilised in 2016) to estimate the PTLD prevalence in SOT patients. This method yields a prevalence estimate of 0.41 per 10,000 persons. On a conservative approach, the sponsor proposes a prevalence estimate of 0.5 per 10,000 persons.

The proposed prevalence would be in line with the most recently accepted figures for the condition. The COMP concluded that the proposed figure of 0.5 in 10,000 persons in the EU could be accepted.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

No treatments for PTLD have been specifically authorised in Europe or other regions or countries at the time of submission of this MAA.

In the absence of approved drugs, guidelines for the management of PTLD have been developed such as the National Comprehensive Cancer Network (NCCN) - Zelenetz 2019, and American Society of Transplantation - Allen 2019, and the British Society of Haematology - Shah 2021. These guidelines include recommendations for the use of EBV-specific CTLs for treatment of EBV+ PTLD, although no such products are currently authorized.

First-line treatment:

Reduction of immunosuppression (RIS) is the first step in the therapy of PTLD. It aims to achieve control of PTLD by the body's own immune system, but without compromising the function of the transplanted organ. With few exceptions, however, the rapid initiation of further therapeutic measures is essential. Where RIS is being considered as the sole initial treatment, response should be assessed

within 2–4 weeks so that alternative strategies can be promptly initiated in those patients that fail to respond. If a complete remission (CR) is obtained, then no other therapy may be required in patients with low risk factors. The European Renal Guidelines have outlined such strategy (EBPG Expert Group on Renal Transplantation. "European best practice guidelines for renal transplantation"; 2002).

Second-line therapy:

Second-line therapy options include cellular therapy (Donor Lymphocyte Infusion - DLI or Cytotoxic T Lymphocyte Therapy - CTLs) or chemotherapy±rituximab (CHOP/R-CHOP). Rituximab, a monoclonal anti-CD20 antibody is used in patients who are unresponsive to initial reduction in immunosuppression standard of care either as monotherapy in both HCT and SOT or as combination therapy with chemotherapy agents, e.g., R-CHOP, in SOT (Shah 2021).

In patients after allogeneic hematopoietic stem cell transplantation, unselected DLI from an EBV-positive donor are employed to restore broad T-cell reactivity, including EBV-specific responses; unselected DLI, however, can be associated with severe GvHD. However, the use of DLI for EBV-PTLD is not recommended in any line of therapy in the most recent National Comprehensive Cancer Network non-Hodgkin lymphoma treatment guidelines (NCCN NHL Guidelines, 3.2016)

The international phase 2 PTLD-1 trial established sequential therapy of 4 cycles of weekly intravenous (IV) rituximab at standard dose (375 mg/m2) followed by 4 cycles of standard dose CHOP-21 chemotherapy (50 mg/m2 doxorubicin; 750 mg/m2 cyclophosphamide, 1.4 mg/m2 vincristine, 50 mg/m2 prednisolone) every 21 days alongside mandatory granulocyte colony-stimulating factor (G-CSF) (Trappe 2012). Although some patients benefit from chemotherapy, it is associated with a high treatment-related mortality (Trappe 2017) and both short and long-term adverse effects (Children's Oncology Group 2018; Watson 2019). Treatment options for paediatric patients with PTLD follow the same treatment algorithms as adults with generally similar outcomes.

In the applied EBV+ PTLD, standard of care for first-line therapy is rituximab, either as monotherapy in HCT or mostly as a combination therapy with chemotherapy agents (e.g., R-CHOP) in SOT. Patients whose disease is relapsed/refractory after treatment with first-line therapy have limited treatment options.

The treatment goal is resolution of all signs and symptoms of PTLD, including a negative viral load. Response to rituximab therapy can be identified by a decrease in EBV DNA levels of at least 1 log10 in the first week of treatment.

Responses to first-line therapy are not durable in most cases. In the HCT setting, approximately 50% of cases fail initial treatment. In patients who fail initial therapy, disease progression is usually rapid with poor outcomes (Dharnidharka 2021; Sanz-Caballer 2021).

Ebvallo is indicated patients with relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) who have received at least one prior therapy and in this second line setting no products are specifically authorised. Therefore, the existing methods described above are regarded as not satisfactory.

Significant benefit

Not applicable.

4. COMP position adopted on 19 October 2022

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of post-transplant lymphoproliferative disorder (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.5 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening due to fulminant and lethal course of the disease and chronically debilitating due to transplant-specific organ dysfunction, malaise, lethargy, weight loss and fever;
- at present, no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Ebvallo.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Ebvallo, allogeneic Epstein-Barr virus specific cytotoxic T lymphocytes, for treatment of post-transplant lymphoproliferative disorder (EU/3/16/1627) is not removed from the Community Register of Orphan Medicinal Products.